Preparing and Submitting Summary Reports for Marketed Drugs and Natural Health Products

Guidance Document for Industry

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Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

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Foreword

Guidance documents are meant to provide assistance on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and eff[illegible].

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with relevant sections of other applicable guidance documents.

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1 Introduction

1.1 Scope and Application

This guidance document provides market authorization holders (MAHs) with information on how to comply with the *Food and Drugs Act*, the *Food and Drug Regulations*, and the *Natural Health Products Regulations* with respect to preparing and submitting annual summary reports (ASRs) and issue-related summary reports (IRSRs).

An ASR is a comprehensive assessment of all known safety information for a marketed drug or natural health product. It is prepared by the MAH to provide an update on the worldwide safety profile at defined intervals post-authorization.

An IRSR is a concise, critical analysis, requested by the Minister, of a specific safety or effectiveness issue. It is prepared by the MAH at the request of Health Canada.

The principles and practices outlined in this document apply to the following products[1] for human use:

- pharmaceutical drugs (which includes prescription and non-prescription drugs);
- biologics as set out in Schedule D to the *Food and Drugs Act* (which include biotechnology products, vaccines and fractionated blood products);
- radiopharmaceutical drugs set out in Schedule C to the *Food and Drugs Act;*
- natural health products as defined in Section 1 of the *Natural Health Products Regulations;* and
- combination products (drug and device).

Blood and blood components and cells, tissues and organs are excluded.

This guidance document **does not** apply to summary reports provided to pre-market Directorates as part of a submission for authorization or to fulfil a condition of market authorization.

1.2 Objectives

This guidance document is intended to:

- clarify Health Canada's expectations for preparing ASRs and IRSRs; and
- provide an overview of the procedures for submitting ASRs and IRSRs to Health Canada.

1.3 Background

According to the World Health Organization (WHO), pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Health Canada encourages and monitors good pharmacovigilance practices (GVP) by industry. MAHs have primary responsibility for the safety of their products and must comply with all Canadian legislative and regulatory

requirements. Health Canada has a responsibility to enforce Canadian legislative and regulatory requirements and monitor risks associated with marketed products.

In addition to Canadian legislative and regulatory requirements, Health Canada aligns with international best practices wherever possible. Health Canada, as an official member to the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH) is committed to the adoption and implementation of ICH guidances.

In 1996, ICH endorsed the ICH E2C Guidance on *Clinical Safety Data Management: Periodic Safety Update Reports (PSURs) for Marketed Drugs*, which provided guidance on the format and content of safety updates. The ICH E2C(R1) harmonized periodic safety reporting requirements for MAHs and provided a common international format. On April 1, 2010, Health Canada adopted ICH E2C(R1) and implemented a two year risk-prioritized PSUR Regulatory Review Pilot. Since that time, the science of pharmacovigilance has evolved globally, prompting reassessment of the role of the PSUR in the spectrum of safety documents submitted to regulatory authorities.

In December 2012, ICH finalized the ICH E2C(R2): *Periodic Benefit-Risk Evaluation Report (PBRER)* Guidance. On March 1, 2013, Health Canada announced to stakeholders that it had adopted ICH E2C(R2). This guidance is intended to ensure that worldwide safety experience is provided to authorities at defined times after marketing, with maximum efficiency and avoiding duplication of effort. The PBRER format will allow MAHs to prepare a comprehensive, cumulative, concise, and critical analysis of new or emerging information on the risks and benefits of their products and to enable an evaluation of the product's overall benefit-risk profile.

2 Annual Summary Reports

Products regulated under the *Food and Drug Regulations*

In accordance with section C.01.018 of the *Food and Drug Regulations*[2], the MAH must, on an annual basis and whenever requested by the Minister of Health, conduct a concise, critical analysis of the adverse reactions (ARs) and serious adverse reactions to a drug and prepare a summary report relating to the reports received during the previous twelve months.

When preparing the report, the MAH must determine whether or not there has been a significant change (see 2.4 below) in the benefit-risk profile of the drug. The current interpretation of benefit-risk profile is a reflection of the overall balance of the product's potential benefits with its identified risks as revealed through safety and efficacy evidence, and through consideration of how that evidence contextualizes with real world conditions of use on the market.[3] If the MAH concludes that there has been a significant change in the benefit-risk profile, they must notify the Minister without delay, in writing, unless this has already been done. The primary focus should be on the clinical significance of such a change.

ASRs are not expected to discuss quality/ Good Manufacturing Practices (GMP) problems unless they result in adverse clinical outcomes. GMP related safety issues should be distinguished from ingredient related safety issues.

If Health Canada determines that an examination of the safety and/or effectiveness of a drug are warranted, a request may be made to the MAH under C.01.018(5) and (6) of the *Food and Drug Regulations* to submit an ASR, and/or the case reports (Council for International Organizations of Medical Sciences [CIOMS] preferred) of all adverse reactions that are known to the MAH.

Products regulated under the *Natural Health Products Regulations*

In accordance with the *Natural Health Products Regulations*[4], the MAH/licensee must, on an annual basis, prepare and maintain a summary report that contains a concise and critical analysis of all domestic ARs to a natural health product, and all foreign serious unexpected ARs to a natural health product, reported during the previous twelve months. If the Minister has reasonable grounds to believe that the natural health product may no longer be safe when used under the recommended conditions of use, the Minister may request any summary reports, interim summary reports and all adverse reactions for which a case report is required, to be submitted to Health Canada within 30 days after the day on which the request is received by the MAH/licensee.

2.1 Preparing and Maintaining Annual Summary Reports

The MAH or a suitable contracted party[5] must ensure that all regulatory requirements of the *Food and Drug Regulations*, and/or the *Natural Health Products Regulations* are met. For further guidance with respect to drug post-market reporting requirement responsibilities of the MAH and the importer, refer to Health Canada's *Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)* (see Appendix 4).

The requirement to prepare ASRs begins on the date that the MAH first sells[6] the product in Canada.
The selected 12-month period for the ASR is specified by the MAH. It is the preference of Health Canada that ASRs be prepared with harmonized Data Lock Points (DLPs) based on the International Birth Date[7] (IBD) of the active

substance. If the MAH is unable to identify the IBD, they should refer to the EU reference dates (EURD) list[8]. For natural health products, the date of first licensing in Canada may be used.

These reports are to be submitted to Health Canada under certain circumstances:

- Upon request by Health Canada;
- To fulfill a commitment.

Health Canada expects that a copy of the ASR be provided with the notification letter if the report shows that there has been a significant change to the benefit-risk profile.

All ASRs must be maintained by the MAH on site or be easily accessible and, when requested, be submitted to Health Canada within 30 calendar days unless otherwise specified.

Health Canada requests that relevant unique Canadian identifiers (DIN, DIN-HM, NPN) be included in ASR reports, to make it easier to link the report to other information about the marketed product.

2.2 Acceptable Annual Summary Report Formats

Depending on the nature of the product and the preference of the MAH, a number of formats are considered to be acceptable for the preparation of ASRs.

The information included in the ASR will vary depending on the adverse reaction data known to the MAH. If a section cannot be completed, this should be noted and explained.

For the preparation of any ASR or IRSR, Health Canada expects MAHs to verify the completeness of their records with the Canada Vigilance Adverse Reaction online Database, for purposes of complete information for assessment. More information on obtaining cases from the Canada Vigilance Adverse Reaction online Database is available on the Health Canada Web site[9].

Acceptable formats for the preparation of ASRs include:

2.2.1 Periodic Benefit-Risk Evaluation Report (PBRER) Format

Health Canada prefers that MAHs prepare ASRs in the Periodic Benefit-Risk Evaluation Report (PBRER) format in accordance with the standards defined in the ICH E2C(R2)[10] guidance. PBRERs should be prepared annually using the time interval for submission (i.e., between data lock point and preparation) outlined in the ICH E2C(R2) guidance. For further guidance on the format and content of a PBRER please refer to the ICH E2C(R2) guidance document[10]. Health Canada may continue to request additional sections of information, if required (e.g. line listings).

2.2.2 Periodic Safety Update Report (PSUR) Format

The Periodic Safety Update Report (PSUR) format, in accordance with the standards defined in the ICH E2C(R1) guidance, is also acceptable to Health Canada. Unless otherwise specified by Health Canada, PSURs

should be prepared annually using the time interval for submission (ie., between data lock point and preparation) outlined in the ICH E2C(R1) guidance, which is available from Health Canada on request.

2.2.3 Non-ICH Annual Summary Report Format

It is also acceptable to prepare an ASR using a non-ICH format that takes into account not only adverse reaction reports but also other sources of information that might be necessary for the analysis. This would include: consumer complaints involving side effects (symptomatic events) and publicly available information (e.g., social media or media reports involving side effects).

MAHs should include in their analysis, where available: information regarding emergent safety issues (e.g. foreign regulatory Web sites, scientific literature pertaining to the product and/or suspect ingredient(s), and actions from other MAHs regarding comparable products). The collection of this information forms part of ongoing post-market safety monitoring by MAHs (environmental scanning). The appropriate timing, frequency and nature of environmental scanning would depend on such factors as the risk profile of the product, any known or specific emergent issues, the scheduling of the summary report, etc. Identified and potential safety issues, as well as knowledge gaps (e.g., toxicity in vulnerable groups, interactions with other products, emergent use patterns) may require more active monitoring.

The preparation of an ASR should result in increasing cumulative knowledge of the product's safety from real-world use, as assessed in relation to available reference safety information (e.g., product monographs, core company data sheets, or core company safety information, also referred to as "global reference safety information").

Even for products with well-established safety profiles, safety issues may emerge. The depth of analysis needed for the ASR depends on the nature and amount of the information collected. ASRs summarize and integrate new cumulative safety knowledge gained from experience during the reporting period.

Health Canada expects that non-ICH format ASRs contain the following sections:

- Introduction
- Summary of changes (if any) to what is known about the product's safety, based on information collected during the reporting period.
- Core reference safety information, preferably Company Core Safety Information (CCSI)/ Company Core Data Sheet (CCDS), if available. If these are not available, other documentation that reflects the core safety knowledge of Canadian authorized products should be included such as the product monograph, or approved labelling information/ terms of market authorization. The type of document should be identified.
- Information about significant domestic or foreign regulatory actions (if any) bearing on safety during the reporting period.
- Patient exposure (see ICH E2C(R2) for details)[10], including Canadian exposure. Basic information would include sales information.
- A critical analysis to determine if there has been, since the last reporting period, an overall change to the safety profile of the product, considering, where applicable:

- Any significant change in the characteristics of expected adverse reactions and/or the overall safety profile (e.g., severity, outcome, target population, changes in effectiveness, use patterns)
- Serious unexpected reactions, placing into perspective the cumulative reports since marketing
- Non-serious unexpected reactions in vulnerable sub-populations
- An increased reporting frequency of expected reactions, including comments on whether it is believed the data reflect a meaningful change in AR occurrence
- Significant changes in post marketing reporting rates, including consideration of patient exposure
- Any new safety issues identified for the following:
  - interactions, including drug interactions
  - experience with overdose, deliberate or accidental, and its treatment
  - drug abuse, misuse, or off-label use
  - positive or negative experiences during pregnancy or lactation
  - experience in vulnerable sub populations (e.g., children, elderly, organ impaired)
  - effects of long-term exposure

- Other information needed for the analysis (e.g., safety-related consumer complaints, information related to effectiveness, late-breaking information, product- or issue specific information, publicly-available safety information)
- A conclusion as to whether there has been a significant change in what is known about the risks and benefits during the period covered by the report
- Adverse reactions line listing(s) (See Appendix 5 for Line Listing(s)), and summary tabulations

MAHs are encouraged to use Medical Dictionary for Regulatory Activities (MedDRA)[11] terminology to analyse and present data.

The ASR should be prepared within 70 days from the data lock point. The ASR must accurately reflect the actual collection and analysis performed and the information used.

An ASR may be prepared as a cumulative summary from the date of first licensing (NHPs) or sale in Canada.

2.2.4 Natural Health Product Annual Summary Report Format

The requirements for annual summary reporting in the *Natural Health Product Regulations* are different from those in Division 1 of the *Food and Drug Regulations* (see Appendix 1: Legislation and Regulations Pertaining to Annual Summary Reports and Issue-Related Summary Reports). Although the ICH format is preferred for the preparation of ASRs, a simpler format is also acceptable for annual summary reports for NHPs.

MAHs should include in their analysis, where available, information regarding emergent safety issues pertaining to the product and/or its ingredient(s). The collection of this information forms part of ongoing post-market safety monitoring by MAHs (environmental scanning). The appropriate timing, frequency and nature of environmental scanning would depend on such factors as the risk profile of the product, any known or specific emergent issues, the scheduling of the summary report, etc. Identified and potential safety issues or knowledge gaps (e.g., toxicity in vulnerable groups, interactions with other products, or emergent use patterns) may indicate a need for more active monitoring.

The preparation of an ASR should result in increasing cumulative knowledge of the product's safety from real-world use, as assessed in relation to available reference safety information (e.g., product and ingredient monographs, core company data sheets, core company safety information, also referred to as "global reference safety information").

Even for products with well-established safety profiles, safety issues may emerge. The depth of analysis needed for the ASR depends on the nature and amount of the information collected. ASRs summarize and integrate new cumulative safety knowledge gained from experience during the reporting period.

Health Canada expects that non-ICH format ASRs prepared for NHPs contain the following sections:

- Introduction
- Summary of changes (if any) to what is known about the product's safety, based on information collected during the reporting period.
- Core reference safety information, preferably Company Core Safety Information (CCSI)/ Company Core Data Sheet (CCDS), if available. If these are not available, other documentation that reflects the core safety knowledge of Canadian licensed products should be included such as the product monograph, or approved labelling information/ terms of market authorization. The type of document should be identified.
- Information about significant domestic or foreign regulatory actions (if any) bearing on safety during the reporting period
- Patient exposure (see ICH E2C(R2) for details)[10], including Canadian exposure. Basic information would include sales information.
- A critical analysis covering:
    - All known adverse reactions occurring inside Canada
    - Serious unexpected adverse reactions inside or outside Canada during the previous 12 months at a dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying organic functions in humans.
- A conclusion regarding the product's real world safety

MAHs are encouraged to consider the following when preparing the critical analysis:

- Changes in the characteristics of expected adverse reactions and/or the overall safety profile (e.g., severity, outcome, target population, changes in effectiveness, use patterns)
- Serious unexpected reactions, placing into perspective the cumulative reports since marketing
- Non-serious unexpected reactions in vulnerable sub-populations
- An increased reporting frequency of expected reactions
- Significant changes in post marketing reporting rates, in consideration of patient exposure
- Additional factors for example:
    - interactions, including those with drugs or other NHPs
    - experience with overdose, deliberate or accidental, and its treatment
    - abuse, misuse, or off-label use
    - positive or negative experiences during pregnancy or lactation
    - experience in vulnerable sub populations (e.g., children, elderly, organ impaired)
    - effects of long-term exposure

- Other information needed for the analysis (e.g., safety-related consumer complaints, information related to effectiveness, late-breaking information, product or issue specific information, publicly available safety information)

MAHs are encouraged to append adverse reactions line listing(s) (See Appendix 5 for Line Listing(s)), and summary tabulations.

The information included in the ASR will vary depending on the adverse reaction data known to the MAH. If a section cannot be completed, this should be noted and justified citing reasons, including but not limited to, e.g. a lack of significant new information.

MAHs are encouraged to use Medical Dictionary for Regulatory Activities (MedDRA)[11] terminology to analyse and present data.

The ASR should be prepared 70 days from the data lock point. In any case, the ASR must accurately reflect the actual collection and analysis performed and the information used.

An ASR may be prepared as a cumulative summary from the date of first licensing in Canada.

2.3 Canadian-Specific Sections

Although standardized periodic summary reports (i.e. PBRERs and PSURs) are used globally, regional differences may exist. Manufacturers should consider the need for a Canadian-specific section when preparing an ASR for submission to Health Canada. Canadian specific data includes:

- Adverse drug reactions occurring in Canada;
- Information such as the epidemiology of the medical condition(s) or risk factors that reflect the authorized indication(s) in Canada in cases where it varies from the authorized indication(s) in other jurisdictions;
- References to the latest available version of the Terms of Market Authorization (e.g., Canadian Product Monograph (CPM); information present in the Licensed Natural Health Product Database[12]; finished product labelling);
- Information related to Canadian patient exposure;
- Post-marketing experience in the Canadian context;
- A discussion of pharmacovigilance activities within the Canadian context;
- Verification of AR records against Health Canada's Canada Vigilance Database; and
- Information that is applicable to the Canadian context, in relation to risk minimization strategies and evaluation of effectiveness of risk minimization activities.

Canadian-specific section(s) can be prepared in the form of a Canadian-specific summary report or as an appendix or annex to an already prepared summary report.

2.4 Notifying Health Canada of a Change in the Risks and Benefits

In accordance with section C.01.018 of the *Food and Drug Regulations*[2], in preparing the ASR, the MAH must determine whether there has been a significant change in what is known about the risks and benefits of the drug. If

the MAH concludes from the ASR that there has been a significant change, they must inform Health Canada immediately in a letter sent to the Office of Submissions and Intellectual Property (OSIP) (See Appendix 3 for contact information), unless this has already been done. The notification should include the most recent completed ASR, and a cover letter indicating that the information is being sent pursuant to the reporting requirements detailed in C.01.018(4) of the *Food and Drug Regulations*. The Marketed Health Products Directorate (MHPD) may request additional information as a follow-up to such a notification.

For natural health products, in addition to complying with regulatory requirements to report safety and efficacy information, Health Canada encourages MAHs to inform MHPD, without delay, if the MAH concludes from the ASR that there is a significant change in what is known about the risks and benefits of a natural health product.

Examples of a significant change in what is known about the risks and benefits of a product include, but are not limited to, a significant change in the frequency or severity of a known risk (e.g., a sudden increase in reporting of QT prolongation), or the identification of a previously unknown serious risk (e.g., a new risk of liver failure, emergent off label uses).

If there are questions as to what constitutes a significant change, please contact the relevant bureau for advice (refer to Appendix 3 for contact information).

2.5 Use of Foreign Reviews

When submitting ASRs to Health Canada, reviews of periodic summary reports or equivalent, or reviews or safety assessments of a specific adverse reaction completed by regulatory authorities in the United States (US Food and Drug Administration) or the European Union's centralized procedure (European Medicines Agency) should also be provided if available. Ideally this would occur at the time of submission of the ASR. If the foreign review becomes available in a reasonable time frame following submission please inform the responsible bureau of its availability. The use of reviews from other foreign regulatory authorities may also be considered if they are in English or French.

2.6 No Adverse Reactions during a Reporting Period

If there are no ARs received by the MAH within a reporting period, an ASR should still be prepared and maintained on an annual basis, including all relevant sections. In any case, Health Canada expects that MAHs verify the information in the Canada Vigilance database. If case reports exist in the Canada Vigilance database, these should be included in the ASR.

3 Issue-Related Summary Reports

Health Canada may require at any time that the MAH perform an analysis of a specific safety or effectiveness issue of a drug by requesting that an IRSR be submitted for the specific safety issue. For example, an IRSR may be requested as a follow-up to a PSUR or PBRER review or as a stand-alone targeted analysis.

Pursuant to section C.01.019(1) of the *Food and Drug Regulations*, Health Canada may, for the purposes of assessing the safety and effectiveness of a drug, request in writing that the manufacturer submit an IRSR. An IRSR contains a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to a drug that are known to the manufacturer with respect to a specific issue that the Minister directs the manufacturer to analyse. The Minister shall, after giving the manufacturer an opportunity to be heard, specify a period for the submission of the report that is reasonable in the circumstances. Typically, a 30 day period is requested for the submission of the report; however, the period may be shorter than 30 days if the information is required on an expedited basis in order to determine whether the drug poses a serious and imminent risk to human health.

There are no provisions in the *Natural Health Products Regulations* for IRSRs. However, for the purposes of assessing the safety and effectiveness of natural health products, Health Canada may request in writing that the MAH submit an IRSR.

3.1 Acceptable Issue-Related Summary Report Format

The information requested in an IRSR should contain, but is not limited to, the following:

- Medical definition of the adverse reaction(s) relating to the subject of the report.
- Description of the search strategy to retrieve the cases (e.g., from databases).
- Detailed summary analysis of the cases. Information should include, but not be limited to: tabulation of all events; MAH comments on the cases; summary analysis of the temporal relationship between product administration and the occurrence of the event; and summary analysis of possible risk factors and confounding variables.
- Canadian and international patient exposure data using both patient-years and total number of patients exposed, if data are available.
- Core reference safety information e.g., (Company Core Safety Information, Company Core Data Sheet), finished product labels, other documentation, such as a product monograph, labelling standard or approved labelling information, which reflects the Canadian market entry requirements.
- A conclusion as to the safety and/or the effectiveness of the product with regards to the occurrence of these events and if applicable, any planned risk mitigating actions or change to the Risk Management Plan, Product Monograph, or labelling.
- Copy of all the Council for International Organizations of Medical Sciences (CIOMS) reports for the adverse reaction of interest reported with the use of the product since its international birth date, if not already submitted. If the volume of CIOMS reports is large and this becomes prohibitive, contact the requesting bureau to discuss options.

In certain instances, additional information may be requested, which would be stipulated in Health Canada's letter to the MAH.

4 Submission Procedures for Annual Summary Reports and Issue-Related Summary Reports

Annual summary reports and issue-related summary reports should be provided to Health Canada in electronic-only format. The submissions should be provided in either English or French.

4.0.1 eCTD Format Requirements

Health Canada strongly recommends that electronic documents be provided in electronic common technical document (eCTD) format. ASRs and IRSRs provided in eCTD format should be prepared using applicable sections of the *Guidance Document: Preparation of Drug Regulatory Activities in Electronic Common Technical Document (eCTD) Format* (see Appendix 4) published on the Health Canada Web site.

4.0.2 Non-eCTD Format Requirements

Alternatively, Health Canada will also accept electronic documents in "non-eCTD electronic-only" format. ASRs and issue-related summary reports provided in "non-eCTD electronic-only" format should be prepared using applicable sections of the *Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format* (see Appendix 4) published on the Health Canada Web site.

4.1 Status Requests

For drugs, MAHs are able to access information about their own submissions via the Drug Submission Tracking System - Industry Access (DSTS-IA).

MAHs with questions about the status or progress of their submission may contact the relevant bureau (see Appendix 3 for contact information). Information will be provided to MAHs in keeping with the confidentiality of the process and without pre-empting the final decision of Health Canada on the disposition of the submission.

Appendix 1: Legislation and Regulations Pertaining to Annual Summary Reports and Issue-Related Summary Reports

The sections of the applicable legislation and regulations that set out the summary reporting requirements including but not limited to annual summary report and issue-related summary reports are listed below.

Food and Drugs Act
Definitions: drug

Food and Drug Regulations
Definition of ADR - C.01.001(1)
Prohibition - C.01.016
Serious Adverse Drug Reaction Reporting - C.01.017
Annual Summary Report and Case Reports - C.01.018
Issue-related Summary Reports - C.01.019
Maintenance of Records - C.01.020
New Drugs - C.08.001, C.08.002(1), C.08.007, C.08.008

Natural Health Products Regulations
Interpretation 1(1):
adverse reaction
natural health product
Section 24

Appendix 2: Glossary

Adverse reaction (AR)
For the purpose of this guidance document, adverse reaction means a noxious and unintended response to a marketed health product covered by this document, and includes "adverse drug reaction" as defined in the *Food and Drug Regulations*[2] and "adverse reaction" as defined in the *Natural Health Products Regulations*[1].

Drug
According to the *Food and Drugs Act*[13], a drug includes any substance or mixture of substances manufactured, sold or represented for use in:

a. the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
b. restoring, correcting or modifying organic functions in human beings or animals, or
c. disinfection in premises in which food is manufactured, prepared or kept.

European Union Reference Date (EURD)
The European Union reference date corresponds to the date of the first marketing authorization of a medicine containing that active substance or that combination of active substances in the EU, or alternatively the earliest of the known dates of the marketing authorizations for a medicine containing that active substance or that combination of active substances.

International Birth Date (IBD)
The date of the first marketing authorization for any product containing the active substance granted to any company in any country in the world.

International Council for Harmonisation (ICH)
The International Council for Harmonisation is a joint regulatory-industry initiative pertaining to the international harmonisation of regulatory requirements for drug products. This is carried out via the development and implementation of harmonised technical guidelines and standards for the development, registration and surveillance of pharmaceutical products. Health Canada is committed to the adoption and implementation of ICH guidances.

Market authorization holder (MAH)
For the purpose of this guidance document, market authorization holder (MAH) means the entity that holds the Notice of Compliance, the Drug Identification Number (DIN), the Natural Product Number (NPN), the Homeopathic Medicine Number (DIN-HM), or the product licence.

Natural health product (NHP)
A substance set out in Schedule 1 of the *Natural Health Products Regulations*[1] or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1 of the *Natural Health Products Regulations*, a homeopathic medicine or a traditional medicine that is manufactured, sold or represented for use in

a. the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
b. restoring or correcting organic functions in humans; or

c. modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

However, a natural health product does not include a substance set out in Schedule 2 of the Natural Health Products Regulations, any combination of substances that includes a substance set out in Schedule 2 of the Natural Health Products Regulations or a homeopathic medicine or a traditional medicine that is or includes a substance set out in Schedule 2 of the Natural Health Products Regulations.

Periodic Benefit Risk Evaluation Report (PBRER)
The PBRER is a pharmacovigilance document intended to provide a comprehensive, concise, and critical analysis of new or emerging information on the risks of the product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. The updated ICH E2C(R2) guidance ensures that annual summary reports for marketed products have the role of being periodic benefit-risk evaluation reports by covering: Safety evaluation, evaluation of all relevant available information accessible to MAHs and benefit-risk evaluation.

Pharmacovigilance
Defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

Periodic Safety Update Report (PSUR)
The PSUR represents a practical and achievable mechanism for summarizing interval safety data, and for conducting an overall safety evaluation. It is a tool for MAHs to conduct systematic analyses of safety data on a regular basis. In addition to covering ongoing safety issues, the PSUR should also include updates on emerging and/or urgent safety issues, and major signal detection and evaluation that are addressed in other documents (ICH E2C(R1).

Serious adverse reaction
For the purpose of this guidance document, serious adverse reaction means a noxious and unintended response to a product covered by this document that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, results in persistent or significant disability or incapacity, is a medically important event or reaction, is life-threatening or results in death and includes "serious adverse drug reaction" as defined in the *Food and Drug Regulations*[2] and "serious adverse reaction" as defined in the *Natural Health Products Regulations*[4].

Terms of Market Authorization (TMA)
The Terms of Market Authorization (TMA) are comprised of all labelling information (e.g., CPM, prescribing information, inserts) that accompanies the Notice of Compliance (NOC) and/or in the document that assigns a DIN, and any related labelling material for drugs. This information is derived from the review of information that is submitted for regulatory review and authorization, as required by the *Food and Drugs Act*, and respective Regulations (and as interpreted by guidance documents and policies).

For natural health products, the TMA is all labelling information (e.g., risk information) that accompanies the product licence and/or document that assigns an NPN or DIN-HM, and any related material for labelling of the natural health product.

Appendix 3: Contact Information

Health Canada is open to discussing specific issues or questions should the need arise.

Drugs

Annual summary reports and issue-related summary reports for drugs must be submitted to the OSIP as per the transmission sections of the eCTD and "non-eCTD electronic-only" guidance documents. Submissions in eCTD format must be sent via the Common Electronic Submissions Gateway (CESG)

Submissions in "Non-eCTD Electronic-Only" format should be sent on media to the following address:
Office of Submissions and Intellectual Property (OSIP)
Health Products and Food Branch, Therapeutic Products Directorate
Health Canada
Address Locator 0201A1
101 Tunney's Pasture Driveway
Ottawa, ON K1A 0K9

Natural Health Products

Annual summary reports and issue-related summary reports for natural health products must be submitted to the Marketed Biologicals, Biotechnology and Natural Health Products Bureau within the MHPD within 30 calendar days of a request by the Minister. MAHs are requested to send their information and material to the following address:

Marketed Biologicals, Biotechnology and Natural Health Products Bureau
Marketed Health Products Directorate
Health Canada
Address Locator 1906A
200 Eglantine Driveway
Ottawa, ON K1A 0K9

Review Bureau Contact Information

Marketed Health Products Directorate:

Marketed Pharmaceuticals and Medical Devices Bureau
E-mail: hc.mpmdb.rpm-bppmmc.gpr.sc@hc-sc.gc.ca
Telephone: 613-946-5140
Facsimile: 613-952-6011

Marketed Biologicals, Biotechnology and Natural Health Products Bureau
E-mail: hc.mbbnhpb.rpm-gpr.bpbbsnc.sc@canada.ca
Telephone: 613-948-6011
Facsimile: 613-954-2354

General Inquires

If you have any questions or comments about the above messaging, please do not hesitate to contact MHPD for clarification. All inquiries pertaining to this Guidance should include the phrase: "Preparing and Submitting Summary Reports for Marketed Health Products Guidance", in the subject line.

Email: mhpd_dpsc@hc-sc.gc.ca

For inquiries related to electronic format, please contact Health Canada using the following e-mail address: E-mail: ereview@hc-sc.gc.ca

Appendix 4: List of Relevant Guidance Documents

MAHs should refer to the most up-to-date versions of the following Guidance documents. This list is provided as a starting point to help manufacturers, and is not exhaustive.

Health Canada Guidance Documents and Notices

- Guidance for Industry: Management of Drug Submissions
- Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document (eCTD) Format
- Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format.
- Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format
- Guidance for Industry: Creation of the Canadian Module 1 Backbone (eCTD)
- Canadian Module 1 Schema Version 2.2
- Notice: Adoption of the International Council for Harmonisation (ICH) Guidance on Periodic Benefit Risk Evaluation Report - ICH Topic E2C(R2), as of March 1, 2013
- Reporting Adverse Reactions to Marketed Health Products
- Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)
- Guidance for Industry: Risk Classification of Good Pharmacovigilance Practices (GVP) Observations (GUI-0063)

International Council for Harmonization (ICH) Guidance Documents

- ICH E2C(R2): Periodic Benefit-Risk Evaluation Reports (PBRERs)
- ICH E2C(R1): Periodic Safety Update Reports (PSURs)

Appendix 5: Line Listing(s) and Summary Tabulations

Health Canada expects that the following types of cases will be included in the line-listing and that attempts will be made to avoid duplicate reporting of cases from the literature and regulatory sources:

- For drugs, from unsolicited sources:
  - all domestic and foreign serious ARs
  - all domestic and foreign non-serious unexpected ARs
  - domestic cases of unusual failure in efficacy for new drugs
- For drugs, from solicited sources where there is a reasonable possibility that the drug caused the adverse reaction:
  - all domestic and foreign serious ARs
  - domestic cases of unusual failure in efficacy for new drugs
- For drugs, from regulatory authority sources:
  - all domestic and foreign serious ARs
  - domestic cases of unusual failure in efficacy for new drugs
- For natural health products, from unsolicited sources and regulatory authority sources, and from solicited sources where there is a reasonable possibility that the natural health product caused the adverse reaction:
  - all domestic ARs to a natural health product
  - all serious unexpected foreign ARs to a natural health product taken at the recommended dose.

The line listing(s) should include each patient only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious AR as judged by the MAH. It is possible that the same patient may experience different ARs on different occasions (e.g., weeks apart during a study). Such experiences would be treated as separate reports. Under such circumstances, the same patient might then be included in a line-listing more than once, and the line-listings should be cross-referenced when possible. Cases should be organized (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

- MAH case reference number
- Country in which the case occurred
- Source of report (e.g., clinical trial, literature, spontaneous, regulatory authority)
- Age and sex of patient
- Daily dose of suspected product (and, when relevant, dosage form or route)
- Date of onset of the reaction
- Dates of treatment
- Description of reaction (current MedDRA terminology is recommended)
- Patient outcome (at case level) (e.g., resolved, fatal, improved, sequelae, unknown). This field does not refer to the criteria used to define a "serious" AR. It should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.
- Comments, if relevant (e.g., causality assessment if the MAH disagrees with the reporter; concomitant products suspected to play a role in the reactions directly or by interaction; indication treated with suspect product(s); dechallenge/rechallenge results if available).

Depending on the product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

An aggregate summary for each of the line listings should be presented. These tabulations ordinarily contain more terms than patients. It is useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for expected and unexpected reactions; other breakdowns might also be appropriate (e.g., by source of report). When the number of cases is very small or the information inadequate for any of the tabulations, a narrative description, rather than a formal table, is considered suitable.

References

1. For the purposes of this guidance, "product" will include those listed in the scope.
2. *Food and Drug Regulations*, Part C, Division 1, C.R.C., c. 870. http://laws-lois.justice.gc.ca/eng/regulations/C.R.C._c._870/index.html
3. Progressive licensing glossary.
4. *Natural Health Products Regulations*, Section 24, Reaction Reporting, C.R.C., SOR/2003-196 http://laws-lois.justice.gc.ca/eng/regulations/SOR-2003-196/index.html
5. There may be instances when the MAH chooses to engage in a contractual agreement with another party whereby they carry out certain activities on behalf of the MAH (e.g., maintaining records related to adverse reaction data and conducting pharmacovigilance activities, including preparing and/or submitting ASRs). In these cases, it remains the responsibility of the MAH to ensure that any documents requested by Health Canada are sent accordingly. For further guidance on GVPs with respect to drug post-market reporting requirement responsibilities of the MAH and the importer, refer to Health Canada's *Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)*. https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/pharmacovigilance-guidelines-0102.html
6. Sell: Includes offer for sale, expose for sale, have in possession for sale and distribute, whether or not the distribution is made for consideration. Sec. 2, *Food and Drugs Act* http://laws-lois.justice.gc.ca/eng/acts/f-27/
7. The date of the first marketing authorization for any product containing the active substance granted to any company in any country in the world.
8. European Medicines Agency, European Union reference dates and submission of periodic safety update reports.
9. Canada Vigilance Adverse Reaction Database; https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html
10. Guidance Document - *Periodic Benefit-Risk Evaluation Report (PBRER)* International Council for Harmonisation (ICH) Topic E2C(R2); https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/periodic-benefit-risk-evaluation-report-pbrer-international-conference-harmonisation-topic.html
11. About the Medical Dictionary for Regulatory Activities; https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database/about-medical-dictionary-regulatory-activities-canada-vigilance-adverse-reaction-online-database.html
12. Licensed Natural Health Products Database; https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/applications-submissions/product-licensing/licensed-natural-health-products-database.html
13. *Food and Drugs Act*: http://laws-lois.justice.gc.ca/eng/acts/f-27/